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(54) **A permselective asymmetric membrane suitable for i a hemodialysis and a process for manufacturing said membrane.**

(57) A permselective asymmetric membrane suitable for hemodialysis, hemodiafiltration and hemofiltration of blood, comprised of a hydrophobic first polymer, a hydrophilic second polymer and suitable additives.

The membrane is characterized by a three-layer structure, comprising a first layer in the form of dense rather thin skin, responsible for the sieving properties, a second layer in the form of a sponge structure, having a high diffusive permeability and serving as a support for said first layer, and a third layer in the form of a finger structure, giving the membrane a mechanical stability.

A process for the manufacturing of the above membrane is also described.

Fig. 1a

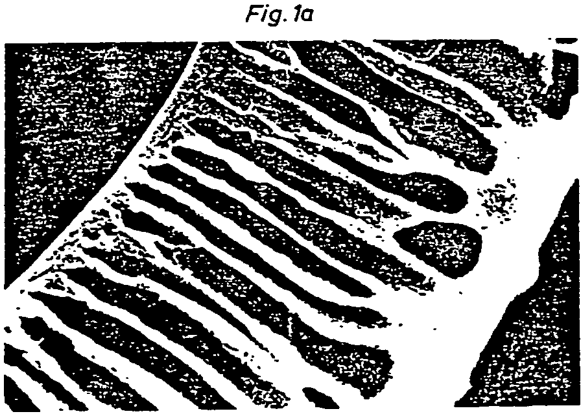
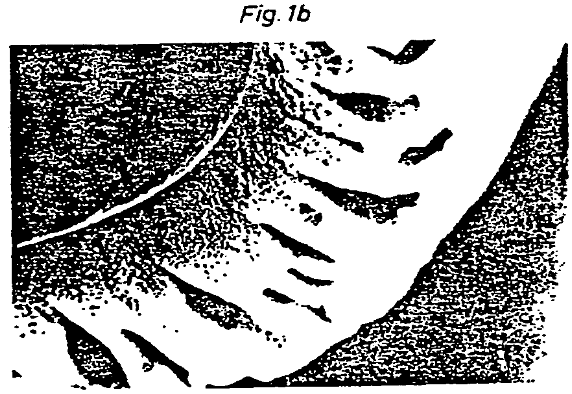


Fig. 1b



EP 0 305 787 A1

A PERMSELECTIVE ASYMMETRIC MEMBRANE SUITABLE FOR I A HEMODIALYSIS AND A PROCESS FOR MANUFACTURING SAID MEMBRANE

TECHNICAL FIELD

The present invention relates to a permselective asymmetric membrane suitable for for example hemodialysis, comprised of a hydrophobic first polymer, a hydrophilic second polymer and suitable additives, and to a process for manufacturing such a membrane.

Membranes of the above kind present special advantages when they are used in connection with different kinds of medical treatments, such as hemodialysis, hemofiltration, plasmapheresis and immunotherapy. They may, however, also be used in connection with dialysis and filtration in general, for example in connection with cleaning or depyrogenization of water.

TECHNICAL STANDPOINT

Membranes of the above kinds are described in detail in for instance EP-A-0 168 783, EP-B-0 082 433 and WO 86/00028. The contents of said publications are therefore included in the present application by reference.

DESCRIPTION OF THE INVENTION

An object of the present invention is to improve membranes of the above mentioned kind by creating a special integral three-layer structure comprising a first layer in the form of a dense rather thin skin, responsible for the sieving properties, a second layer in a form of a sponge structure, having high diffusive permeability and serving as a support for said first layer, and a third layer in the form of an open finger structure, giving the membrane a mechanical stability. The advantages obtained by such a structure will be explained more in detail in the following.

As regards possible compositions, properties and other characteristics of the membrane reference is made to the following claims.

The invention relates also to a process for manufacturing a membrane of the above kind, characterized in that the hydrophobic first polymer is presolved in a solvent, the hydrophilic second polymer is presolved in a solvent of preferably the same kind and in that the two solutions are mixed, whereafter the mixture is introduced into a precipitating liquid to obtain a coagulated membrane, which is subsequently washed and preferably dried.

As regards how said process may be carried through more in detail, reference is made to the following claims.

Due to the fact that the present invention in the first place is intended to be used to improve a membrane essentially of the kind described and claimed in the above mentioned EP-B-0 082 433 it will in the following be described more in detail in connection with such a membrane and how it may be manufactured.

BRIEF DESCRIPTION OF DRAWINGS

Fig 1a and 1b show scanning electromicroscopic pictures of the membrane structure.

Fig 2a and 2b show more in detail the skin and the porous layer.

Fig 3 shows the sieving coefficients for two different membranes in vivo and in vitro, respectively, one membrane being made in accordance with the invention and the other outside the protection scope for comparison.

Fig 4 presents the results of protein adsorption measurements on the same two membranes.

Fig 5 shows the increase of the complement factor C_{3a} during the first period of a dialysis treatment for four different membranes (any such increase has not been observed for a membrane according to present invention).

Fig 6 shows the change of the number of leucocytes in a patients blood by hemodialysis by the use of a membrane according to the present invention.

Fig 7 shows the ultrafiltration rate of a membrane according to the present invention at different trans membrane pressures and different blood flows.

Fig 8, finally, shows the urea clearance for a membrane according to the present invention at different blood flows.

BEST MODE OF CARRYING OUT THE INVENTION

The manufacturing of the membrane according to the present invention follows a phase inversion process, where a polymer or a mixture of polymers is solved in a solvent. The solution is then extruded through a spinning nozzle (for hollow fibers) or a slit nozzle (for flat film) into a fluid bath containing a nonsolvent for the polymer. The nonsolvent replaces the solvent and thus the polymer is precipitated to an inverted solid phase.

For the membrane of the present invention the hydrophobic polymer, the hydrophilic polymer and an additive are mixed in the following way:

a) the hydrophobic polymer, preferably polyamide, is presolved in a solvent, preferably DMSO (dimethylsulfoxid).

b) the hydrophilic polymer, preferably PVP (polyvinylpyrrolidone), is separately premixed in a solvent, preferably DMSO. a) and b) are thereafter mixed together at an elevated temperature, preferably 60 °C, and high shear forces or with ultrasonic equipment. Then the solution must be cooled, preferably below 21 °C.

If this process is not followed the PVP will form aggregates. During the membrane forming process this PVP-aggregates will precipitate and be washed out leaving microholes in the membrane.

Before the extrusion any possible additives are mixed into the mixture of a) and b). The additives are used to form a proper pore structure and optimize therewith the membrane permeability, the hydraulic and diffusive permeability and the sieving properties. The additives may be said to work as pore controller. Substances which may be used are nonsolvents or weak solvents for the hydrophobic polymer, preferably alcohols, glyceroles and water.

To provide a hollow fiber according to the present invention the above mixture is extruded through a nozzle with two concentric openings. Through the outer ring slit the polymer solution is extruded, through the inner core opening the centre fluid, a nonsolvent of the hydrophobic polymer, is extruded. The fiber is then immersed in baths of nonsolvents or fluids which can replace and wash out the solvent. As solvent there are preferably used polar solvents like DMF, DMSO or DMAc.

To achieve an optimal structure in a membrane according to the invention (3 integral layers) the center fluid (for a hollow fiber), respectively, the first precipitation fluid bath (for a flat film) should be a mixture of the hydrophilic polymer, an additive and a solvent, i e mixed with the nonsolvent. It has been found that with this constellation (center fluid and the described polymer solution) the typical integral 3-layer structure is formed. Depending on the ratio of the components the 3 layers get different thicknesses.

EXAMPLE 1

In accordance with the above defined manufacturing technique 13 w% polyamid was dissolved into a solution containing 3 w% PVP (MW 100 000), 3 w% water and 81 w% DMSO. The polymer solution was degassed and filtered, and then pumped through a concentric hollow fiber spinning jet. The polymer was extruded through the outer ring slit with an outer diameter of about 0,35 mm and an inner diameter of about 0,25 mm. From the inner orifice of the jet a solution of 30 % DMSO, 3 % PVP and 67 % water was extruded.

A hollow fiber was thus formed with 215 μ inner diameter and 50 μ wall thickness. The fiber was then washed thoroughly with non-pyrogenic water, then treated with a mixture of 40 % glycerol and 60 % water, and finally dried with air.

The membrane formed got a structure of 3 layers: the inner dense skin with a thickness of about 1 μ, the sponge-like substructure with a thickness of about 5 μ and the open finger-like structure with a thickness of about 45 μ.

EXAMPLE 2

12 w% polyamid was solved as described above in 85 w% DMSO together with 1% PVP and 2% H_2O. The polymer solution was cast with a slit jet on a belt and transported through a precipitation bath containing 68 % water, 2 % PVP and 30 % DMSO. The flat membrane got a thickness of 60 µ . After washing, glycerolization and drying the membrane could be winded without support.

EXAMPLE 3

Membranes (hollow fibers) manufactured as described in example 1 were assembled in a dialyzer with 1,3 m^2 surface area. The ultrafiltration with water was measured to be 250 ml/mm $Hg.m^2.h$. With whole blood the ultrafiltration was dependant on flow parameters and blood composition (hematocrite Hct, protein concentration Pct, blood flow and transmembrane pressure), and is influenced by protein concentration polarization. At a blood flow of 300 ml/min a maximum ultrafiltration of 120 ml/min was achieved with blood of 25 % Hct and 65 g/l total protein (see fig 7).

The diffusive permeability is estimated by the clearance. Clearances for urea, measured in blood for a dialyzer according to example 3 with blood flows of 200, 300 and 400 ml/min are shown in fig 8. The ultrafiltration at this occasion was prohibited to 0. The total protein in the filtrate was less than 0,05 g/l filtrate.

The β_2-M permeability was measured in clinical use for the same dialyzer by measuring the concentration of β_2-M in the venous (C_v) and arterial (C_a) blood stream and in the filtrate (C_F).
The calculated sieving coefficient

$$S = \frac{2c_F}{C_v + C_a}$$

was 0,65. Rejection of endotoxins released (from E-coli) was measured with suspensions loaded (challenge) with 1,25 ng/ml E-coli endotoxins. The LRV was 4,0 (definition see below).

EXAMPLE 4

A solution of 13% PA, 3% PVP, 3% H_2O and 81% DMSO was spun with a centre fluid of 90% H_2O, 1%PVP and 9% DMSO to a hollow fiber of dimensions mentioned in example 1. The hollow fiber got the 3 layer integral structure typical for the present invention. The sieving coefficient - measured with plasma containing 65 g/l total protein concentration - for β_2-M was measured to be 0.8. In spite of this high sieving coefficient for β_2-M the sieving coefficient for the total protein was below 0.001.

EXAMPLE 5

A solution of 11% PA, 1% PVP, 3% H_2O and 85% DMSO was spun with a centre fluid of 98% H_2O and 2% PVP to a hollow fiber of the dimensions mentioned in example 1. The sieving coefficient for β_2-M was measured in plasma to be 0.62 and for total protein below 0.001.

GOAL OF THE INVENTION

A membrane with a asymmetric structure characterized by 3 integral layers with different functions and structure:

a) a smooth and dense homogenous thin (preferably <1 µ) layer, which determines the sieving properties.

b) a porous (sponge like) layer (preferably about 1-15µ) which determines the mechanical stability of the inner layer (a) and acts as safety barrier in case the layer (a) has a defect.

ULTRAFILTRATION

Hemodialysis, hemodiafiltration and hemofiltration membranes are characterized also by their ultrafiltration permeability (other expressions are hydraulic or mechanical permeability, or convective permeability). For hemofiltration and hemodiafiltration a high ultrafiltration rate is desired. The membrane according to the present invention shows much higher ultrafiltration rate for water (about 250 ml/h mmHg.m^2, measured at 37°C) than most other membranes. The membrane according to EP-A-0 082 433, for example, is reported to show a lower ultrafiltration rate (200 x 10^{-3} 1/m^2.d.bar, corresponding to 110 ml/h.mmHg.m^2)

SIEVING PROPERTIES

Membranes for hemodialysis and hemofiltration on one hand need the described high permeability and on the other hand must reject proteins with high molecular weight. For albumin (MW 68 000) the rejection should be infinite The patient would otherwise loose essential proteins.

Recent clinical investigations give, however, indications that a protein with low molecular weight (β_2-M, MW 11 500) should be removed during dialysis treatments because it causes amyloidosis.

With the membrane of the present invention the combination of these two requirements can be fulfilled, i e it is possible to provide a high sieving coefficient (S) of about 0,6-0,8 for β_2-microglobulin, and a low sieving coefficient for albumin of about 0,001. The mentioned sieving properties are measured in clinical treatment on human blood.

$$\text{Definition of } S = \frac{\text{concentration in filtrate of a substance } C_{UF}}{\text{mean value of blood inlet and outlet}} = \frac{C_{UF}}{\frac{C_i + C_o}{2}}$$

The above mentioned sieving characteristics (see fig 3) are achieved because the membrane according to the present invention has a very narrow pore size distribution on the inner membrane skin. In contrary to the membrane according to EP-A-0 168 783 the inner skin membrane layer according to the present invention (which is responsible for the sieving properties) is very thin. The thinner the layer is, the more homogeneous pore sizes can be achieved.

Another advantage of the membrane according to the present invention is that the difference between the sieving coefficients, measured in water (in vitro) and in plasma or whole blood (in vivo), respectively, is small (see fig 3). Fig 3 shows also for comparison the sieving coefficient of a membrane made from the same hydrophobic PA-material but without the addition of the hydrophilic polymer. In that membrane a big difference between 'in vitro' and 'in vivo' sieving is observed.

The reason for the negligible difference of the hydrophilic version is a lower protein adsorption to the membrane. The reduced adsorption of proteins decreases the risk for changing the membrane pore sizes. The adsorption was investigated by a method which is described in the Ritz et al reference mentioned at the end of the present description. Fig 4 presents the results of the adsorption measurements on both types of membranes and shows clearly that much higher amounts of protein can be rinsed back and eluted from the more hydrophobic membrane.

From this result it can be concluded that in the hydrophilic version less proteins are adsorbed on the membrane and in the membrane pores. The effect of this provides a small or no change of the membrane effective pore size and the sieving properties.

As regards fig 4 it may be added for explanation that TBS stands for trisbuffered solution and that part III of this figure shows the qualitative results of the elution of the membrane with three different elution fluids 1 SDS/Triton-solution (sodiumdodecylsulfate), 2 urea solution, 3 natrium-chloride solution. These elution fluids were used after the rinsing procedures shown in part I and II, respectively, to eluate the residual proteins. The SDS/Triton solves hydrophobic/hydrophilic binding sites, urea solves the hydrogen binding sites and NaCl the ionic sites. No proteins could be detected in the solution fluids of the hydrophilic variation (PA/PVP).

c) an open finger like supporting layer, which gives the membrane its mechanical stability for trans-membrane pressures and stresses during manufacturing (handling). This membrane structure shows outstanding properties for the different blood purification methods, such as hemodialysis, hemodiafiltration and hemofiltration, because it has a high diffusive permeability for low molecular weight substances, a high permeability for middle molecular weight substances (MW 1000-15000) like β_2-microglobulin (MW 11 500), an ultrafiltration rate adaptable to hemodialysis, hemodiafiltration and hemofiltration, and an outstanding biocompatibility.

STRUCTURE

When the membrane is manufactured in the form of a hollow fiber, the inner layer or blood side is supposed to be a skin with a thickness of preferably less than 1µ . The pores in this skin are typically in the range 80]. The skin layer determines the sieving and permeability properties. The second layer is supposed to be a sponge-like structure with a thickness of preferably about 5 µ . This layer supports the primary skin layer mechanically and gives the skin a continuous reinforcement and an improved resistance to burst and leakages (pin holes). The third layer shows an open finger-like structure with a thickness of about 20-60 µ , preferably 40µ . The void volume in this part is high and gives low resistance for convective (filtration) and diffusive transport.

Scanning electromicroscopic (SEM) pictures in fig 1a and 1b show the whole membrane structure.

Fig 2a and 2b show more in detail the skin and the porous layer. To get this pictures the membrane had to be prepared in a special way:

a) the frozen membrane was cut in microtom slides

b) the membrane slide was etched and coated with C/Pt (carbon or platinum)

c) the replica was then magnified with SEM. In the above mentioned publication EP-A-0 168 783, a membrane is described for similar applications as the membrane according to the present invention, but with a sponge-like structure through the whole thickness. The inner side of a membrane according to said publications show under the microscope a pore size of about 150]. The pores are then increasing from the inner to the outer side. The disadvantage of such a membrane is that proteins can penetrate into the structure of the membrane and thus change the membrane permeability.

DIFFUSIVE PERMEABILITY

The membrane of the present invention has a high diffusive permeability for substances which are to be removed in hemodialysis. Urea is one of the substances which is used as one of the characterizing test substances. The diffusive permeability Pm, measured (according the method described in NIH Report 77-1294 Evaluation of hemodialyzers and dialysis membranes) in a test cell is much higher than corresponding values measured for a membrane in accordance with the above mentioned publication EP-B-0 082 433. The Pm-values of the membrane according to the present invention are between 110 and 150 x 10^{-5} cm/sec, whereas the above publication report Pm-values of 75 x 10^{-5} cm/sec (45 x 10^{-3} cm/min).

The diffusive permeability Pm of a membrane determines the clearance of a hemodialyzer. The mathematical description of this relationship is :

$$\text{Clearance} = Q_B \cdot \left[1 - e^{Pm \cdot A/Q_D} \right]$$

The high Pm-values of the membrane according to the present invention correspond to clearance values for a 1 m^2-dialyser of 175-185 ml/min at the standard conditions of 200 ml/min blood flow and 500 ml/min dialysate flow and TMP of 0 mmHg measured with whole blood. The high diffusive permeability of the membrane is achieved by the low diffusive resistance of the membrane which is caused by the high degree of hydrophilicity of the membrane and the described open structure.

REJECTION OF BACTERIOLOGICAL MATERIAL

If the membrane is to be used in hemodialysis mode the membrane should reject bacteriological material. It has, however, been found in some clinical studies that e g endotoxins may pass the cellulosic membranes normally used for dialysis and cause fever reactions.

With the membrane of the present invention this risk is reduced by its very high rejection capability of bacteriological material. Endotoxins (from E-coli) are rejected by the membrane with a logarithmic reduction of 3,5-4,5. The reason for this very good rejection for endotoxins and other bacteriological material is that the pore sizes of the inner skin layer is within a very close range and that the maximum pore size does not exceed 80] $\hat{=}$ 0,008 µ .

Definition of the logarithmic reduction value (LRV)

$$\text{e.g. } LRV=\log_{10}\left[\frac{\text{number of organisms in challenge suspension}}{\text{number of organisms in filtrate}}\right]$$

LRV = 3 means: 999 out of 1000 endotoxins are eliminated.

The reduction value for bacteria pseudomonas diminuta stam ATCC 19146 was measured with LRV > 10^7. These bacteria are larger in size, and therefore they are rejected to a higher degree.

BIOCOMPATIBILITY

It is reported that, for example, cellulosic membranes like Cuprophan or saponified cellulose might activate the complement system. This activation can be measured by an increase of the complement factors C_{3a}, C_{3d}, C_{5a}, mainly C_{3a}, during the first 15-20 minutes of the dialysis treatment. Whereas Cuprophan shows an increase of the C_{3a} factor concentration in the patients blood from 10 to 7000 ng/ml (fig 5), there was no increase measured for the membrane according to the present invention when it was made according to the above examples.

Another parameter is the change of leucocyte cells in the blood during the dialysis treatment. Once again, by using Cuprophane membrane, the number of leucocytes in the patients blood drops within the first 15-20 minutes to about 20% of the initial value. Only a small drop to about 90% of the initial value is seen with the membrane made in accordance with the above examples (fig 6).

Presently the C_{3a} factor concentration and the leucocyte changes are used as parameters to characterize biocompatibility. Low changes in these two parameters indicate a good biocompatibility.

REFERENCES

E Ritz, K Andrassy, J Bommer, E Rauterberg:
Protein Layer Formation on artificial membranes;
(C Tegernsee-symposium, March 1986)
Contribution to Nephrology No 50, Karger, Basel

NIH Report 77-1294
Evaluation of hemodialyzers and dialysis membranes

EP-A-0 168 783
EP-B-0 082 433
WO 86/00028

Claims

1. A permselective asymmetric membrane suitable for for example hemodialysis, comprised of a hydrophobic first polymer, a hydrophilic second polymer and suitable additives, **characterized** by a three-layer structure, comprising a first layer in the form of a dense rather thin skin, responsible for the sieving properties, a second layer in the form of a sponge structure, having a high diffusive permeability and serving as a support for said first layer, and a third layer in the form of a finger structure, giving the membrane a mechanical stability.

2.A membrane according to claim 1, **characterized** in that it consists of 85-95% of said hydrophobic first polymer, 0,5-7,5% of said hydrophilic second polymer and 0,5-7,5% of suitable additives.

3. A membrane according to claim 1 or 2, **characterized** in that said hydrophobic first polymer is chosen from the group polyarylsulfone, polycarbonate, polyamide, polyvinylchlorid, modified acrylic acid, polyether, polyurethane, polyacrylnitrile, polypropylene, polyetherimide and copolymers of said polymers, preferably polyamide.

4. A membrane according to any of the claims 1-3 , **characterized** in that said hydrophilic second polymer is chosen from the group polyvinylpyrrolidone, polyethylenglycol, polyglycolmonoester, copolymers of polyethyleneglycol with polypropylenglycol, water soluble cellulosic derivates, polysorbate, and polyethylene-polypropylene oxide copolymers, preferably polyvinylpyrrolidone.

5. A membrane according to any of the preceding claims, **characterized** in that said additives are chosen from the group non-solvents or weak solvents for the hydrophobic polymer, such as alcohols, glyceroles and water.

6. A membrane according to any of the preceding claims, **characterized** in that it has a high sieving coefficient for beta-2-microglobulin with MW of 12 500 (in blood), preferably at least 6, and a high rejection rate for albumin with MW of 68 000, preferably above 99% ($s < 0{,}01$).

7. A membrane according to any of the preceding claims, **characterized** in that the inner layer has a maximum pore size of about 80]ngstr|m.

8. A membrane according to any of the preceding claims, **characterized** in that the inner layer has a thickness less than 1μ .

9. A membrane according to any of the preceding claims, **characterized** in that the second layer has a thickness in the magnitude of about 1-15μ , preferably 3-5 μ .

10. A membrane according to any of the preceding claims, **characterized** in that the 3rd layer has a thickness in the magnitude of 20-60μ , preferably about 40μ .

11. A membrane according to any of the preceding claims, **characterized** in that it has a logarithmic reduction value of at least 3 for the rejection of endotoxins.

12. A process for manufacturing a mebrane of a hydrophobic first polymer and a hydrophilic second polymer and suitable additives, **characterized** in that the hydrophobic first polymer is presolved in a solvent, the hydrophilic second polymer is presolved in a solvent of preferably the same kind and in that the two solutions are mixed, whereafter the mixture is introduced in a precipitating liquid to obtain a coagulated membrane, which is subsequently washed and preferably dried.

13. A process according to claim 12, **characterized** in that the mixing is made under an elevated temperature, preferably about 60°C and in that the extrusion thereafter is made at a lower temperature, preferably below 21°C.

14. A process according to claim 12 or 13, **characterized** in that the mixing is made under high shear forces.

15. A process according to claim 12 or 13, **characterized** in that the mixing is made in combination with an ultrasonic treatment.

16. A process according to any of the claims 12-15 **characterized** in that said solvent is chosen from the group dimethylacetamid, dimethylformamid, dimethylsulfoxid, n-methylpyrrolidon and mixtures of said solvents, preferably dimethylsulfoxid.

17. A process according to any of the claims 12-16, **characterized** in that said precipitating liquid includes a solvent for the second hydrophilic polymer, preferably water.

18. A process according to claim 17, **characterized** in that the precipitation liquid includes a solvent for the first hydrophobic first polymer, preferably DMSO.

19. A process according to any of the claims 17-18, **characterized** in that the precipitation liquid includes a part of the hydrophilic second polymer, preferably PVP.

20. A process according to claim 18, the first polymer being polyamid and the second polymer being PVP, **characterized** in that the precipitation liquid includes about 70% water and 30% DMSO.

21. A process according to any of the claims 12-20 for the manufacturing of a hollow fibre, **characterized** in that a jet of precipitation liquid is extruded within the center of the hollow fibre simultaneously with the mixture of the two polymers.

22. A process according to any of the claims 12-21, **characterized** in that the precipitation is followed by water rinsing, glycerolization and drying.

23. A process according to any of the claims 12-22, **characterized** in that the extrusion solution consists of 78-88% solvent, 10-15% hydrophobic polymer, 0,5-5% hydrophilic and 0,5-5% additives.

24. A membrane according to any of the claims 1-11, **characterized** by a ultrafiltration permeability for water in the magnitude of 250 ml/h.mmHg.m^2.

25. A membrane according to any of the claims 1-11, **characterized** by a diffusive permeability of 110-150 x 10^{-5} cm/s.

Fig. 1a

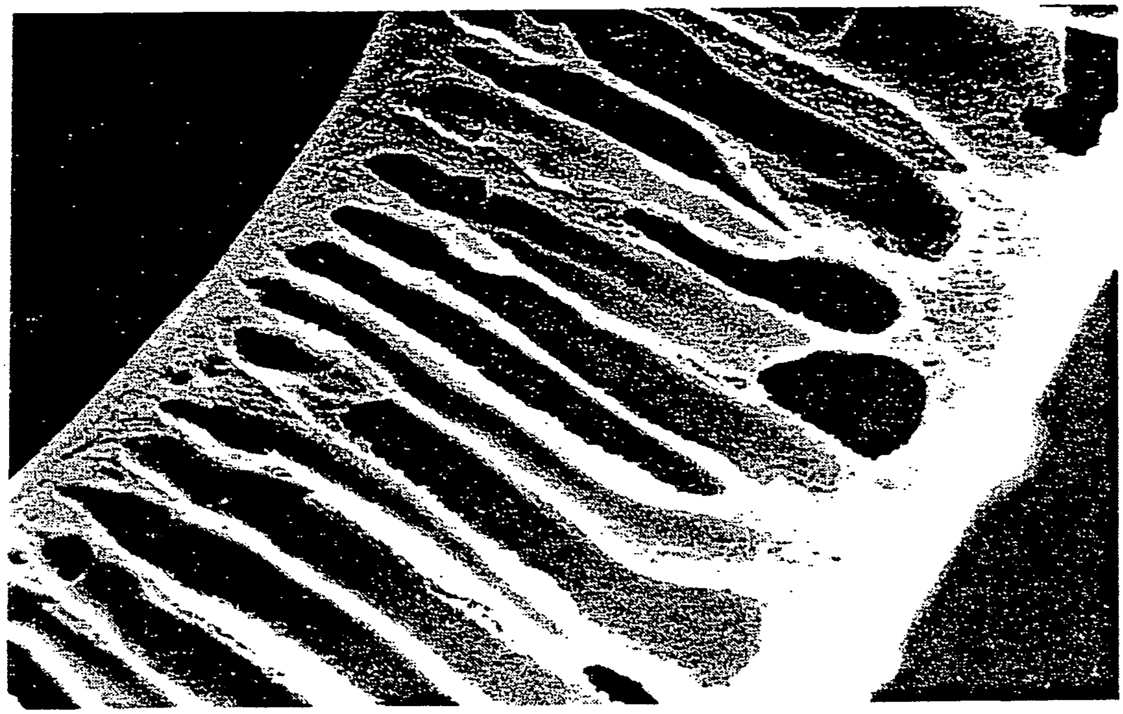


Fig. 1b

Fig. 2a

Fig.2b

Fig. 3

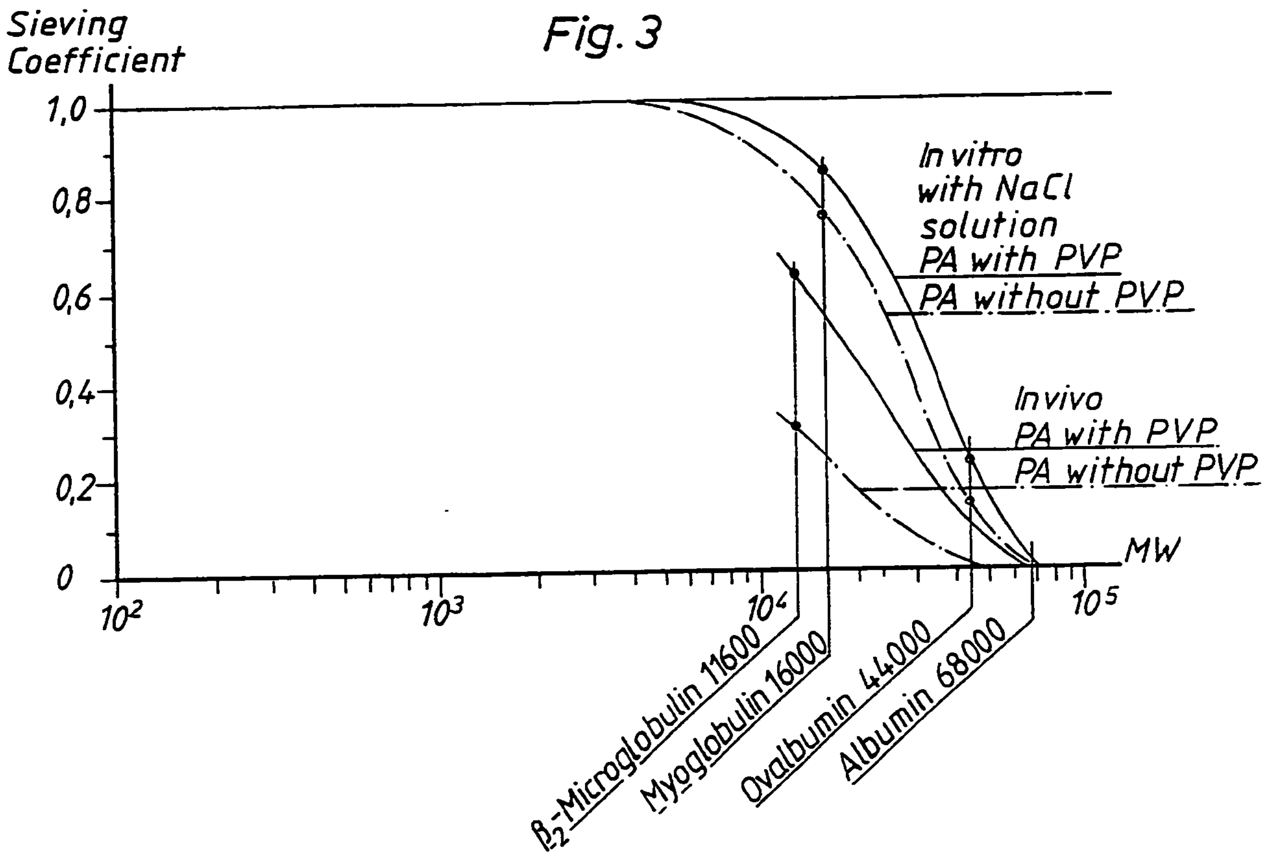


Fig. 4

Protein Concentration in Different Rinsing Cycles and Elution Steps

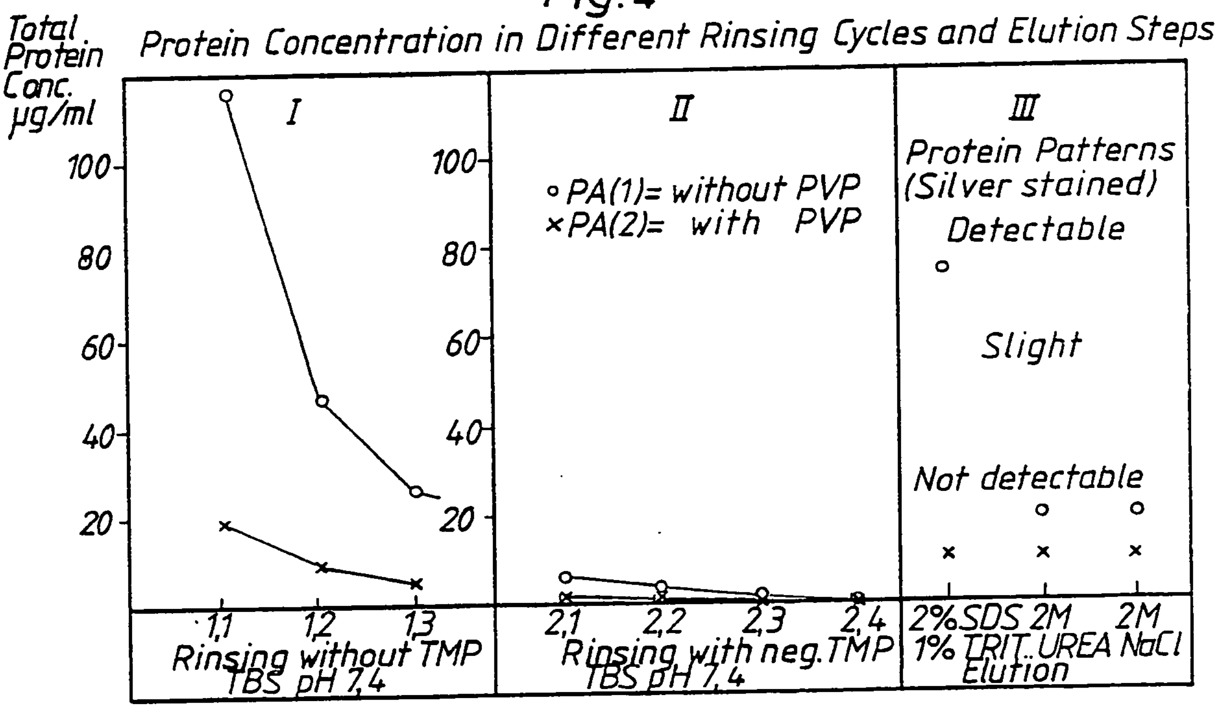


Fig. 5

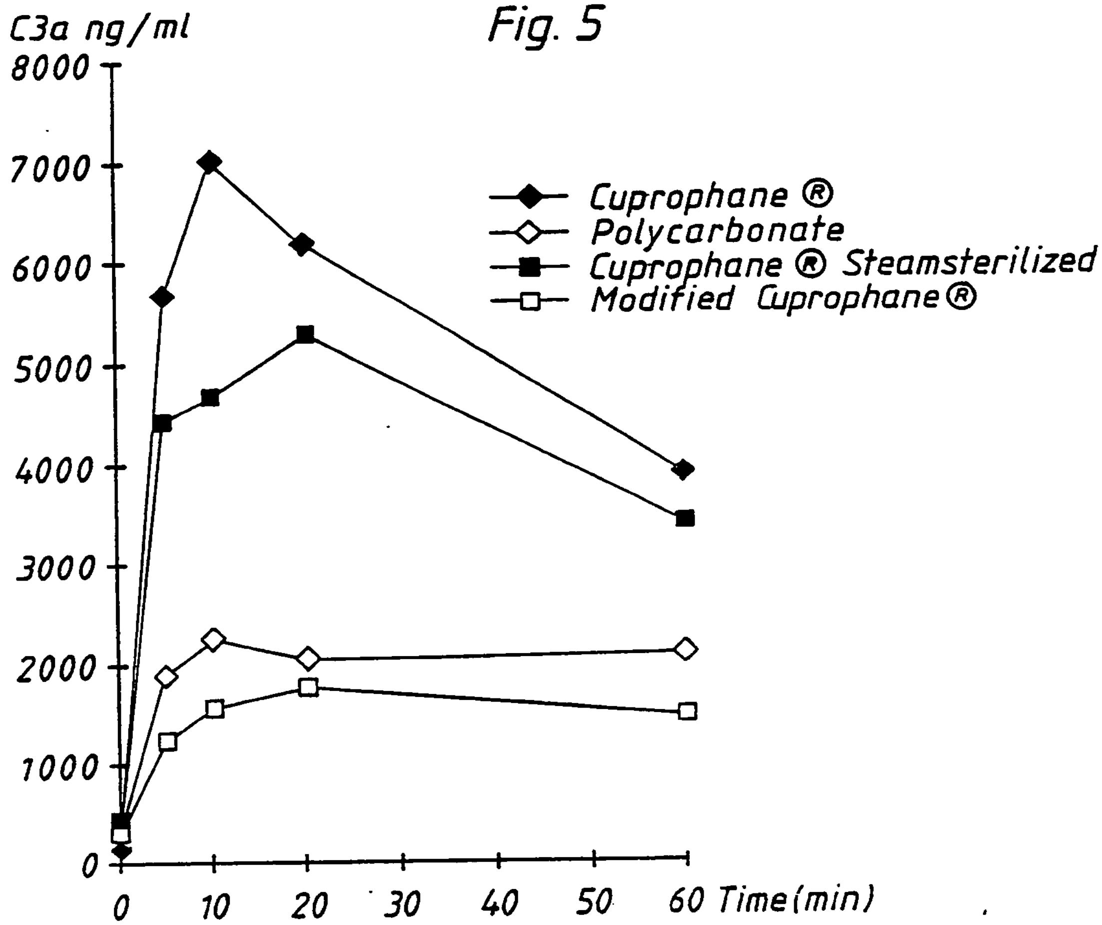

C3a ng/ml
8000
7000
6000
5000
4000
3000
2000
1000
0
0
10
20
30
40
50
60 Time(min)
Cuprophane ®
Polycarbonate
Cuprophane ® Steamsterilized
Modified Cuprophane ®

Fig. 6

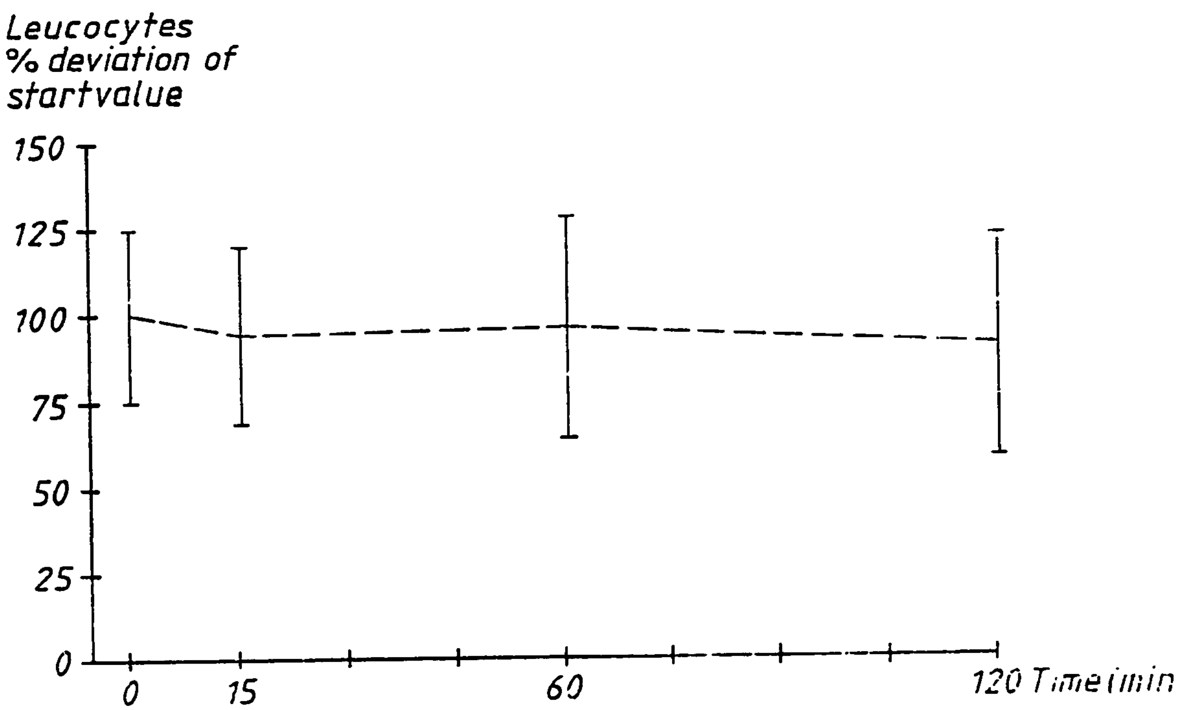

Leucocytes
% deviation of
startvalue
150
125
100
75
50
25
0
0
15
60
120 Time(min)

Fig. 7

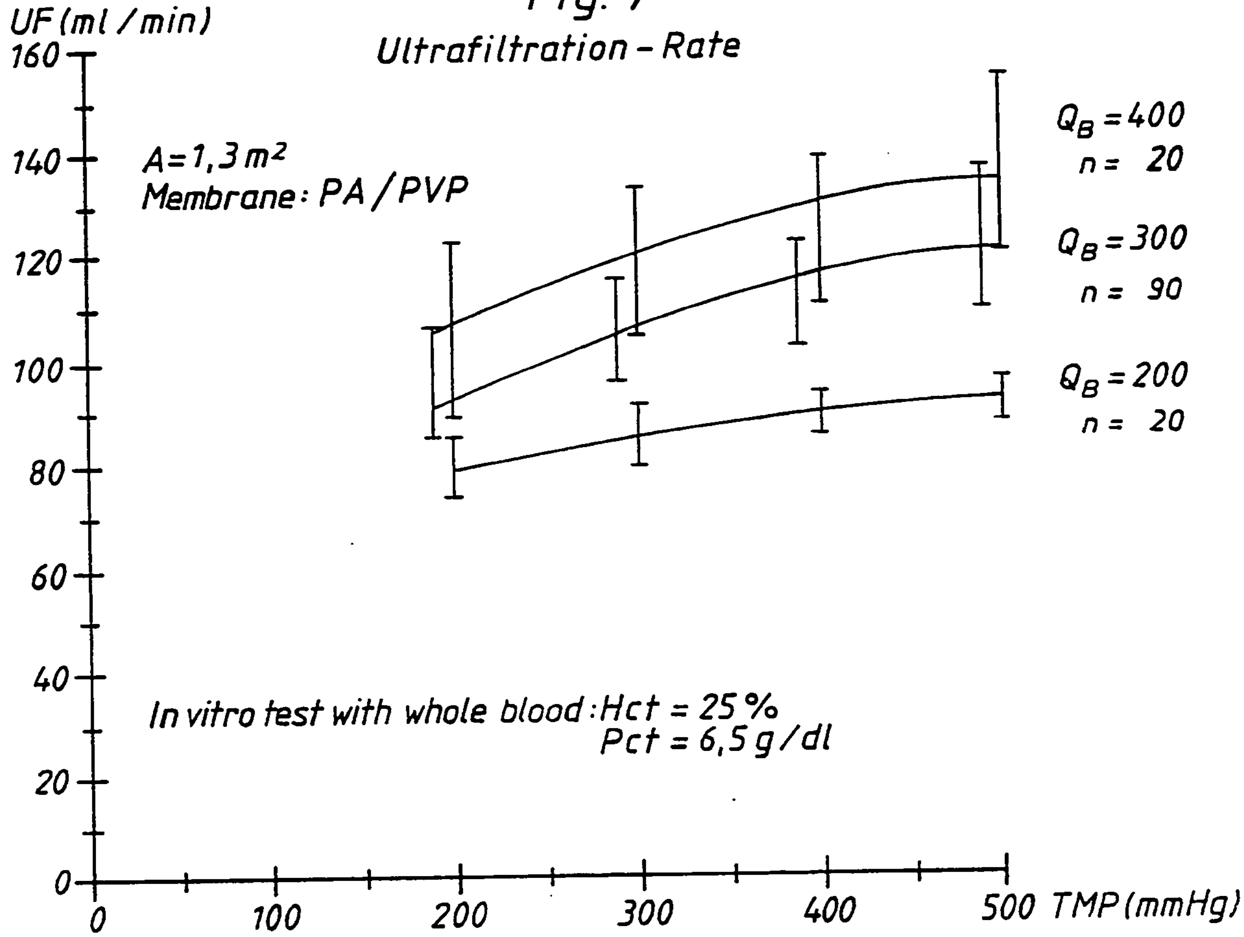
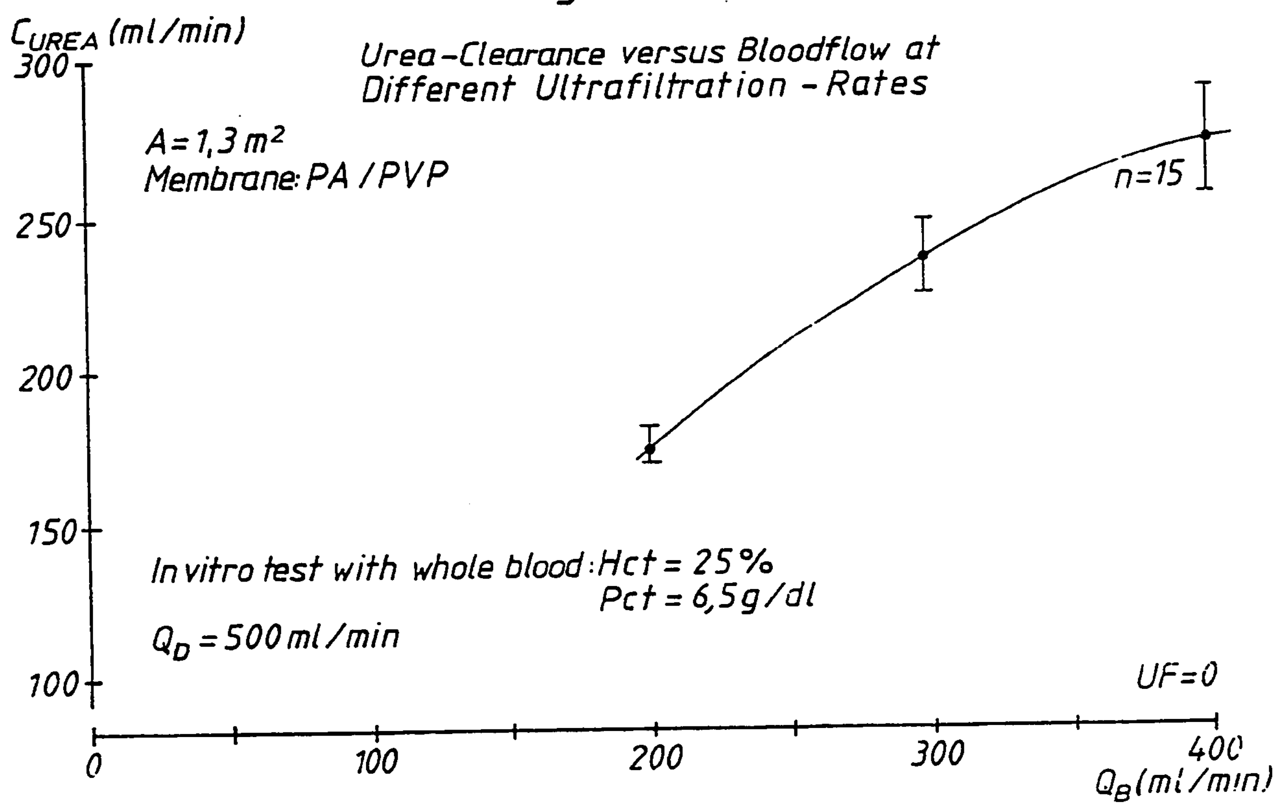

UF (ml / min)
Ultrafiltration - Rate
160
140
120
100
80
60
40
20
0
A = 1,3 m²
Membrane: PA / PVP
Q_B = 400
n = 20
Q_B = 300
n = 90
Q_B = 200
n = 20
In vitro test with whole blood: Hct = 25 %
Pct = 6,5 g / dl
0
100
200
300
400
500 TMP (mmHg)

Fig. 8


C_{UREA} (ml / min)
Urea-Clearance versus Bloodflow at
Different Ultrafiltration - Rates
300
250
200
150
100
A = 1,3 m²
Membrane: PA / PVP
n=15
In vitro test with whole blood: Hct = 25 %
Pct = 6,5 g / dl
Q_D = 500 ml / min
UF=0
0
100
200
300
400
Q_B (ml / min)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 11 3098

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	PATENT ABSTRACTS OF JAPAN, vol. 10, no. 120 (C-343)(2177), 16th May 1986; & JP - 60 246 812 (DAICEL) 06-12-1985 * abstract *	1,3,4, 12,16	B 01 D 13/04
D,X	EP-A-0 168 783 (FRESENIUS AG) * claims 1, 2, 4, 9, 14, 15; page 8, line 23; page 9, lines 1, 2; page 10, lines 3, 8; page 12, lines 34-36; page 13, lines 29, 30; page 14, lines 26-38; page 15, lines 1-7, 18-25; page 17, lines 1-9, 20-26, 31-33; page 18, lines 20-26 *	1-5,8, 12,17, 18,21, 22,24	
D,X	EP-A-0 082 433 (HOECHST AG) * claims 1, 7; page 8, lines 21-27 *	3,4,7,8	
X	US-A-4 051 300 (KLEIN et al.) * claims 1, 3, 5-7 *	3,4,12, 16	
D,X	WO-A-8 600 028 (INSTITUT NATIONAL DE RECHERCHE CHIMIQUE APPLIQUEE) * claims 1, 2, 7-9 *	1,3,4,8	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	DE-A-3 407 252 (KURARAY CO.) * claims 1-3, 7 *	1,3,4,8	B 01 D 13/00 B 01 D 13/04 A 61 M 1/03 A 61 M 1/10 D 01 D 5/24
X	PATENT ABSTRACTS OF JAPAN vol. 11, no. 115 (C-415)(2562), 10th April 1987; & JP - A - 61 257 203 (TERUMO CORP.) 14-11-1986 * abstract *	14	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	22-10-1988	CORDERO ALVAREZ M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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L : document cited for other reasons

& : member of the same patent family, corresponding document